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In re

Patent Application of

Nicholas DeMarco

Application No. 10/775,451

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Examiner: Ernest G. Therkorn

"CHROMATOGRAPHY CARTRIDGE AND METHOD FOR MANUFACTURING A CHROMATOGRAPHY CARTRIDGE"

I, Julie A. Haut, hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date of my signature.

Julie A. Haut
Signature

6/19/07
Date of Signature

DECLARATION OF NICHOLAS DEMARCO UNDER 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Nicholas DeMarco, declare as follows:

1. I am the inventor of the chromatography cartridge claimed in Application No. 10/775,451 (the "'451 Application").

2. I have been President of Analogix, Inc. ("Analogix") since I founded the company in 1998. Analogix is located at 171 Industrial Drive, Burlington, Wisconsin 53105. I have engineered products for the chromatography industry for most of the past nine years since graduating from Milwaukee School of Engineering in 1993 with a Bachelor of Science degree in Manufacturing Engineering. Prior to founding Analogix, I worked for Lida Manufacturing Corporation for three years designing and trouble-shooting chromatography equipment.

3. The chromatography cartridge claimed in the '451 Application includes a tubular housing having two open ends with a plug fused within each of the two open ends. In addition,

a substantial portion of the plugs are fused to an inner surface of the tubular housing in the two open ends.

4. By way of general background, chromatography is a chemical analysis process that involves passing multiple chemical compounds, mixed with one or more solvents, through a column or chromatography cartridge. The chromatography cartridge includes a medium that acts to separate the various components of the chemical compound. As the chemical compound flows through the medium, its different components will adsorb to the medium to varying degrees. The components with strong attraction to the medium move more slowly than those with weak attraction. As a result, the various chemical components will elute from the chromatography cartridge at different times. The chemical components with the least affinity for the medium (the most weakly adsorbed) will elute first, while those with the greatest affinity for the medium (the most strongly adsorbed) will elute last. A detector positioned downstream of the chromatography cartridge can determine the chemical component and generate a chromatogram.

5. As one skilled in the art of chromatography cartridges and chemical analysis equipment, it is my opinion that my chromatography cartridge invention provides a unique solution to a long-felt need in the art and would not have been obvious to anyone of ordinary skill in the art at the time of its invention.

6. **PERSISTENT NEED.** Chromatography was first developed in the early 1900's. Over the years, chromatography has developed to be an invaluable laboratory tool for scientists for the separation and identification of chemical compounds. Today, the separation of chemical compounds is vital in any type of chemical analysis.

7. As technology has advanced, pre-packaged chromatography cartridges were developed to assist scientists in the chemical separation process. The pre-packaged chromatography cartridges were developed using off-the-shelf components that scientists soon discovered leaked and could not withstand the increasing pressures applied to the cartridges as

flow rates increased. In addition, scientists recognized that problems with compaction of the silica within the cartridges contributed to inefficiencies in the chemical separation process.

8. From the early 1970's through about 1993, purification or "flash" chromatography was performed using glass cylinders with fiberglass wool stuffed into one end with silica filling the remaining portion of the glass cylinder. The chemical compound to be analyzed was combined with a solvent, and the mixture was poured into the glass cylinder. By gravitational forces, the mixture would pass through the silica and the fiberglass wool. The various components of the mixture would have different affinities for the silica, and therefore, would elute from the glass cylinder at different times. A scientist would manually monitor the output of the glass cylinder to fill one or more test tubes. The chemical components in the test tubes would be further tested with, for example, thin layer chromatography techniques, to detect the chemical component in the test tube. *W. Clark Still et al., Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution, J. Org. Chem., 2923-2925 (1978).*

9. In about 1993, a company known as Biotage LLC is believed to have been the first to develop a pre-packaged chromatography cartridge. The pre-packaged Biotage cartridge used an off-the-shelf plastic tube, typically used for dispensing glue, that was filled with a frit at the bottom of the tube and a frit at the top of the tube with silica packed between the two frits. In use, the chemical compound to be analyzed was mixed with a solvent and passed through the cartridge.

10. In 1998, when the pre-packaged chromatography cartridge market was relatively small, a company known as ISCO entered the market, along with a company known as Analogix, the assignee of the present invention. Biotage, ISCO, and Analogix are believed to have been the major manufacturers of pre-packaged chromatography cartridges during this period.

11. As pre-packaged chromatography cartridges became increasingly popular over the next several years, scientists demanded larger, more efficient cartridges to accommodate

faster flow rates. With the industry being so new, the financial incentive to design larger and more efficient cartridges was not reasonably large.

12. During this time, Analogix manufactured pre-packaged chromatography cartridges using the same off-the-shelf plastic tube as used in the Biotage cartridge, with a threaded connection for the rear cap that held the frit and the silica in place. The Biotage and Analogix cartridges were often subject to leaks when used in the field by scientists.

13. Also during this time, ISCO manufactured pre-packaged chromatography cartridges using an off-the-shelf syringe barrel with a sonic-welded rear cap that held the frits and the silica in place. The sonic weld bonded the rear face of the syringe barrel to the face of the cap. The weld resisted the tensile forces caused by pressure within the cartridge, and these cartridges worked well under low pressure applications (<45 PSI). However, under higher pressures (50-100 PSI), these cartridges, too, were subject to leaks when used in the field by scientists. Scientists preferred higher pressures because they allow samples to be moved through the cartridge at higher speeds (i.e., higher pressure = higher flow rate). Also, upon being purified, the sample could crystallize. When the sample crystallizes, it plugs the flow of solvent through the system. These plugging events cause high back pressures and are further reason for leak or failure situations.

14. Analogix began looking for ways to resolve this leaking problem for its customers. At this time, the Analogix and ISCO cartridges were manufactured by filling the tube with the two frits and with sufficient silica to still have enough room for the cap to be applied to the tube. Generally speaking, the height of the silica bed (or the amount of silica) was controlled by the cap location. While looking for a solution to the leak problems, I also discovered that the silica beads used in chromatography cartridges do not have a uniform size and shape. As a result, a fixed mass of silica does not always compact to the same volume. The silica bed in the chromatography cartridge loosens to fill the container volume during shipment and/or storage, and therefore, the silica bed is not fully compacted when used by the

scientists. The less-compacted silica beds lead to lower efficiency for scientists because there is less component separation when the silica is not fully compacted. Basically, the liquid mixture finds the path of least resistance and flows through the silica bed with less adsorption to the silica. In essence, the real problem with the cartridges was delivering a pre-packaged product to the scientists with the silica fully compacted. In addition, scientists were asking for larger cartridges to allow them to process larger quantities of each chemical and increase efficiency.

15. Around 2001, Analogix began forging a new path in the design of pre-packaged chromatography cartridges and rejecting conventional wisdom of using off-the-shelf components. I believe that Analogix was the first to design a pre-packaged chromatography cartridge without a single off-the-shelf component. We designed and built dies to extrude the plastic for the housing. We also began experimenting with solutions to the silica bed compaction and leaking issues.

16. As we learned from our customers, the existing ISCO cartridge was not meeting the needs of the scientists as the tensile (or axial) strength of the sonic weld was not holding up to the applied pressures, and therefore, the cartridges still leaked. Based on the common formulas (a) $Area\ of\ circle = \pi * r^2$ and (b) Pressure = Force*Area, it is well known that the separation force between the cap and syringe of the ISCO cartridge would increase dramatically as the diameter increases (assuming the pressure remained constant).

17. ISCO, therefore, began to design a cartridge using 100% custom parts and a design that would simplify the manufacturing process and improve product performance. ISCO's design used cantilevered, integrally molded plastic tangs that snap-fit around the column body. The tangs held the column closed and, in my opinion, simplified the manufacturing process. This ISCO cartridge design is disclosed in U.S. Patent Nos. 6,565,745 and 6,949,194.

ISCO rated the columns to withstand 45 PSI before leaks would occur. However, this cartridge suffers from the loose silica bed after shipment and leakage problems.

18. Biotage's solution to the loose silica bed issue, at this time, was a disposable cartridge using a non-disposable holder with a compression fit metal piston. In addition, Biotage utilized an exotic O-ring in its cartridge to attempt to resolve the leaking problem.

19. In my opinion, ISCO's solution had two deficiencies: a) after snapping the cap in place, the resulting volume within the column was fixed. When filling and compacting the silica, small changes in volume could not be absorbed by the snap-fit design. This meant the silica would loosen in transit. b) The plastic tangs could not resist the forces that tended to separate the cap from the column body under moderate pressures (over 45 PSI), nor were they capable of being scaled up to larger diameters (again, the forces exceeded the practical limits—leading to leaks).

20. In contrast to the ISCO solution, the Analogix cartridge was custom-designed to fuse or spin-weld a plug into the end of the tube. This method of fusing a substantial portion of an outer surface of the plug to a substantial portion of an inner surface of the tube allowed the silica bed to remain compacted during shipment and storage. In essence, the silica bed was compacted and then the plug was spin-welded to the precise height of the silica bed in that particular cartridge, thereby preventing any possibility of shifting of the silica.

21. To further emphasize the important invention of using the spin-welding process with a chromatography cartridge, the spin-welding process can be stopped at varying heights, whereas a similarly designed ultrasonic weld joint must "collapse" a precise distance and stop. The ultrasonic energy imparted to the joint by the ultrasonic process begins to dissipate into the "springiness" of the plastic when the joint sees too much friction. In contrast, the spin welding process is more "flexible." The spinning part will continue spinning so long as the driving element has sufficient torque to overcome friction forces of the joint. Also, in ultrasonic welding, air will be "whipped" into the plastic after the weld continues for an extended time. The air turns

the "to-be-welded" plastic locally to the joint into foamy plastic with little resulting strength. This foaming also limits the practical distance that ultrasonic welding can cover. Spin-welding does not suffer from this problem since the exposed surface is simply a circle, not a flapping plane of plastic.

22. The spin-welding process of fusing the plug to the inside of the tube solved the cartridge leaking problem. By inventing this solution, we are able to manufacture larger cartridges without the silica bed issues and without the leaking problems. Today, cartridges manufactured using the spin-welding process perform satisfactorily for the scientists' purposes. The spin-welded cartridges being used today fail only at pressures greater than 600 PSI, and, furthermore, the failure is within the tubular wall, not in the spin-welded region. In contrast, cartridges manufactured using other methods typically fail at pressures under 100 PSI.

23. This persistent need for a solution to the leaks and larger cartridges has been recognized by those of ordinary skill in the art.

24. **NEED NOT SATISFIED BY ANOTHER.** Second, the need in the art was not satisfied by another before my chromatography cartridge invention. Despite many obstacles, we invented a solution to the need that plagued the scientific chemical analysis industry. Although we have numerous active competitors in the chromatography cartridge industry, including ISCO and Biotage, none satisfied the need before my chromatography cartridge invention.

25. As discussed above, our competitors, ISCO and Biotage, modified their cartridge designs (several times in ISCO's case) to find a solution, but still could not find a solution to both the leaking and the silica bed compaction issues.

26. **INVENTION SATISFIES NEED.** Third, test results in our laboratory confirm that the chromatography cartridge invention satisfies the scientific chemical analysis industry's need described above. We compared the performance of Analogix' spin-welded chromatography cartridge to ISCO's chromatography cartridge. The purpose of this test was to determine the

amount of pressure that the cartridges could withstand before leakage would occur. The test results showed that Analogix' fused or spin-welded chromatography cartridge outperformed the other product tested.

27. The Analogix fused or spin-welded chromatography cartridge provides a larger cartridge for the scientists' required efficiency. The Analogix fused or spin-welded chromatography cartridge is also able to withstand high pressure while preventing leaks and maintaining a compact silica bed.

28. Not only has Analogix received positive customer feedback on the fused or spin-welded design solving the scientists' long-felt need of a leak-proof cartridge and fully compacted silica, we recently discovered that our spin-welded cartridge design is being copied by ISCO. As further evidence of our solution satisfying the need for a larger cartridge and a leak-proof design, ISCO has recently introduced a new cartridge line (the RediSep Rf cartridges) that is advertised to withstand higher pressures for higher efficiency (smaller particle size silica). All of the new ISCO RediSep Rf cartridges are now spin-welded, most likely because ISCO could not develop an alternative technology that satisfied all the needs of the product or market.

29. Actual users of the Analogix fused or spin-welded chromatography cartridge have responded very favorably to our chromatography cartridge invention. Analogix has received considerable feedback from scientists on its cartridges using a fused or spin-welded plug. Furthermore, we have received very few user complaints and returned cartridges on the fused or spin-welded cartridge compared to our cartridges without a fused or spin-welded cap. After introducing our cartridge having a fused or spin-welded cap, we have only had one customer complaint of a leaking cartridge to date. In contrast, during the same time period, we had 32 customer complaints of leaking cartridges that did not have a fused or spin-welded cap.

30. For at least the above reasons, the chromatography cartridge invention is the first to fulfill a long-felt need for a solution to the leaking and silica compaction problems encountered in the scientific chemical analysis industry.

31. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

19-June-2007

Dated

Nicholas DeMarco